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Vaccine trials

Vaccines: hope vs reality

Are the candidate vaccines in late-stage human trials really everything the world has been waiting for, asks **Graham Lawton**

IT IS the ultimate exit strategy from covid-19. A safe and effective vaccine is of "critical importance to world health", the World Health Organization (WHO) has said.

Vaccine developers are working flat out to make good on that. Last week, the US pharmaceutical giant Pfizer and its German partner BioNTech announced positive-looking results from their ongoing phase III trial, the last stage of testing whether a potential vaccine is safe and effective. The interim results showed a headline success rate of 90 per cent, meaning that nine out of 10 trial participants who caught the new coronavirus had received a placebo rather than the vaccine.

"How long will immunity last? The desired answer is 'forever', but realistically a year would be positive"

The news got some people very excited indeed. Asked on BBC radio whether these results meant a probable return to normal by early next year, John Bell at the University of Oxford and a member of the UK government's coronavirus vaccine task force channelled Meg Ryan in *When Harry Met Sally* and said: "Yes, yes, yes!" Many listeners no doubt thought: "I'll have what he's having."

A few days later, another phase III trial – this one being run by the Gamaleya National Center of Epidemiology and Microbiology in Russia – reported even better interim results: a success rate of 92 per cent. And earlier this week, US company Moderna announced 95 per cent efficacy from its ongoing phase III trial (see page 7).

So things look good. But we are still a long, long way from a vaccine that will get us back to life as normal. That is in no small part due to the huge challenge of manufacturing, distributing and administering one (see page 36), plus the reluctance of a significant minority of people to get vaccinated (see page 12). However, it is also down to trial constraints, which leave a number of questions around safety and effectiveness. If you thought those were the things the trials could give us all the answers to, think again.

Complex question

"In my line of work, I get asked this nearly every day from my friends and family: will this particular vaccine or that particular vaccine work?" says Susanne Hodgson at the University of Oxford's Jenner Institute, which researches vaccines. "And I'm always stumped by how to deliver the answer quickly. Because it is a complex question."

The least complex part of the question is, how long will immunity last? The desired answer is "forever", but realistically a year would be a very positive outcome. In April, the WHO published an official assessment of what would constitute a safe and effective covid-19 vaccine. On length of protection, it said its preferred outcome was at least a year, but it would accept a minimum of six months – though pointing out that this "might not be demonstrated in initial clinical studies". The US Food and Drug Administration (FDA) has set the same goal, and the UK vaccine task force says it is prepared to have to vaccinate people twice a year.

As yet, however, even that six-month bare minimum hasn't been attained. The Pfizer and BioNTech phase III study began vaccinating people in late July and has only just finished recruiting volunteers. As a result, it won't have an answer until February at the earliest, because the vaccine requires two shots, three weeks apart. We simply don't know yet how long protection from any vaccine will last.

NATALIA KOLESNIKOVA/AFP VIA GETTY IMAGES

6 months
The minimum protection the WHO requires a vaccine to provide

50%
The lowest acceptable level of vaccine protection set by the WHO

90%
The protection achieved by Pfizer and BioNTech's candidate vaccine, according to early results

Time isn't something that the vaccine developers have control over. But they can control other aspects of trial design, and these raise some major questions, says Peter Doshi at the University of Maryland School of Pharmacy. Last month, he wrote an article in *The BMJ*, of which he is an associate editor, entitled "Will covid-19 vaccines save lives? Current trials aren't designed to tell us."

How is it possible that these trials aren't designed to reveal

A volunteer in Moscow takes part in the trial for the Sputnik V vaccine

whether the vaccines on which we are pinning so much hope will actually save lives?

The problem relates to the trials' so-called "end point", the bar against which success or failure is judged. It is set fairly low. The WHO and FDA have both said they will accept a vaccine that provides at least 50 per cent protection against infection. That means the trials need to show that no more than half as many people who received a vaccine get infected as people who got the placebo.

Putting aside the 90 per cent plus results for now, that isn't good enough, says Doshi. For one thing, the 50 per cent threshold for the trials could mean that a vaccine that is only actually 30 per cent effective makes it through, as the error bars representing uncertainty in the trial data are quite large.

Another issue is that the success rate obtained in a vaccine clinical trial often exceeds that seen in the real world. As Hodgson puts it, "vaccine efficacy does not always predict vaccine effectiveness". There are various reasons for this, she says. A major one is that the deployment of a vaccine on the ground, to millions or billions of people, is much more challenging than administering it within a tightly regimented clinical trial.

That is especially true of a two-shot vaccine that relies on people showing up to two appointments, often weeks apart. For this reason, the WHO says it would prefer a one-shot vaccine. However, all but one of the 12 vaccines in phase III trials require a couple of shots. "I think it would be prudent to anticipate that we may see some differences between covid vaccine efficacy in clinical trials and real-life settings," says Hodgson.

According to Paul Offit, at the University of Pennsylvania and a member of the FDA's Vaccines and Related Biological Products Advisory Committee (VRBPAC), the FDA is likely to accept six months or even less of efficacy data, even though it usually asks for at least two years and most vaccine trials last even longer. Admittedly, this is an emergency and we have to accept some uncertainty, he says, but we need to be ready to be "unpleasantly surprised" by a vaccine that delivers weak or short-lived immunity. And the first vaccine to succeed is rarely the best, he warns.

"We could end up with vaccines that reduce the risk of mild infection but not the risk of death"

Nonetheless, the 90 per cent plus success rates seen so far suggest that these vaccines will easily exceed the 50 per cent threshold, so this issue may just be theoretical. The phase III trials aren't complete yet, but it would take a major reversal to erode those high initial figures. Even with a fall to 80 or 70 per cent, a vaccine's impact would still be far above the WHO's minimum requirement. "Of course, we all want a vaccine which is as efficacious as possible," says Hodgson. "But I think given the scale of the pandemic, the rates of transmission and the morbidity and mortality we're seeing, even a partially efficacious vaccine could have a really significant impact."

Mild cases only

Despite this, the trials aren't going to tell us what, if any, effect a vaccine has on severe illness, according to Doshi and others. On 22 October, he told a VRBPAC hearing that "unless urgent changes are made to the way the trials are designed and evaluated, we could end up with approved vaccines that reduce the risk of a mild infection but do not decrease the risk of hospitalisation, [intensive care unit] use or death."

This seems outlandish, but again it comes down to the trials' end point. In all the phase III trials, this is defined as the prevention of mild covid-19 symptoms, such as a cough, fever, headache or sore throat. Any participants with these symptoms are tested to confirm whether or not they are infected by the SARS-CoV-2 virus. If there are many more such cases in the placebo group than the control ›

How the Pfizer/BioNTech phase III trial works

More than 43,500 people are recruited to the trial

Around half are given a vaccine, half get a placebo. Neither participants nor researchers know who is in which group

When participants report mild symptoms like a cough or fever they are tested for the coronavirus

Once a certain number of people are confirmed as having had covid-19, called a "checkpoint", the results are "unblinded" to reveal whether these positive cases had been given a vaccine or a placebo

So far, of 94 covid-19 cases, 90 per cent were among those in the placebo group

The trial will end when there have been 164 confirmed infections, the final checkpoint

group, we can see that the vaccine is working – in preventing mild cases, at least. But such a result tells us next to nothing about whether the vaccine is stopping infected people from getting really sick. The issue is compounded by these vaccines being tested in a subset of the population that is predominantly young and healthy, and so at relatively low risk of getting severe covid-19.

"In a deadly pandemic, we want to see efficacy data demonstrating a reduction in severe disease and long-term consequences," says Doshi. "Efficacy against a transient, mild illness in relatively healthy people is far less important than protecting the most vulnerable."

He accepts that people who are protected against catching the

"The trials appear designed to answer the easiest questions, not the most important ones"

disease cannot, by definition, go on to develop severe covid-19 or die from it. But that isn't the point. "That is true, if you are talking about a single person. But a vaccine will not have identical efficacy in all populations," he says. "Let's say it works really well in healthy adults, but provides very little protection in frail elderly [people], to choose one high-risk group. In this scenario, your trial can demonstrate an effect against mild disease, but you would still have all the serious cases because the vaccine is not protecting the frail elderly."

More than three-quarters of deaths caused by SARS-CoV-2 infection are in people over the age of 65, but they can be poorly represented in trials.

In the plans for the Pfizer and BioNTech trial, 40 per cent of phase III participants are

JUAN MABROMATA/AFP VIA GETTY IMAGES

A scientist in Argentina working on a vaccine candidate for the region

supposed to be 55 years old or over, but the figures released from the trial don't include an age breakdown. Neither company responded to *New Scientist*'s requests for that information.

The Gamaleya vaccine team told *New Scientist* that people aged up to 60 were vaccinated and included in the data, but again provided no actual numbers.

In any case, people aged 55 or even 60 hardly qualify as "frail elderly", who often have weakened immune systems and don't respond well to vaccines. Age-related decline in the immune system can kick in as early as 55, but there is huge variation from person to person, says Deborah Dunn-Walters, an immunologist at the University of Surrey, UK.

Some of the vaccines that have yet to report any results are being tested in older groups. In the University of Oxford and AstraZeneca vaccine trial, for instance, at least a quarter of participants are over 65.

The Moderna results are more promising because this vaccine was given to people over 65, and some of those who became ill with the disease were in this age bracket.

Another issue is that without regularly testing all participants, a clinical trial could fail to pick up large numbers of asymptomatic infections.

One phase III trial – of the vaccine being developed by the University of Oxford and AstraZeneca, which Hodgson is working on – is testing every participant for the virus each week. As a result, its findings may exclude the possibility of missing lots of asymptomatic infections – at least for its own vaccine, which works in a very different way to Pfizer and BioNTech's and Moderna's.

The decision to omit severe disease as a primary end point is unusual. According to a research paper by an international group of industry, government and academic researchers published late last month in the *Annals of Internal Medicine*, severe disease is an end point "used in virtually all vaccine efficacy trials". The group urged all vaccine developers to include severe covid-19 as an end point in their trials.

Doshi says the trials appear designed to answer the easiest questions in the least amount of time, not the most clinically important ones.

It is possible to do a covid-19 clinical trial with severe disease as an end point, says Hodgson, but it would be a major undertaking because that outcome is still quite rare. "The studies do not have adequate numbers of patients to be able to reliably tell us if they prevent severe disease," she says. "We will need to give these vaccines to much larger populations in order to collect

Phase IV trials

Once vaccines are approved, they are usually closely monitored to detect any rare but potentially serious side effects that the trials were too small to spot. This evaluation, often called a phase IV trial, usually runs for a year or two because rare adverse reactions may take months or even years to be detected, says Susanne Hodgson at the University of Oxford.

One rare but serious problem is "vaccine enhanced disease", in which vaccinated people who go on to catch the virus their vaccine targets become more ill than they would have without the vaccine. It occurs when the immune response elicited by a vaccine backfires and actually helps the virus cause disease rather than hinder it.

Hodgson says this was seen in animal experiments on vaccines for SARS and MERS, diseases caused by coronaviruses closely related to SARS-CoV-2, the virus behind covid-19.

"But importantly, this hasn't been seen in the animal models of covid-19 vaccines to date, and there's no signal yet that we've seen anything like this in the clinical trials ," she says.

It is also worth noting that Pfizer and BioNTech's and Moderna's vaccines use an unproven technology (see page 14), rather than being based on the usual viral proteins or weakened form of the pathogen – so they could spring new surprises down the road.

that kind of data and get that output."

Pfizer has said that it and BioNTech are collecting data on severe disease as a secondary end point – but the numbers still aren't big enough. Hodgson says this may be an issue for all the trials. "It's unlikely that they're going to have sufficiently sized trials to reliably get an indication about whether vaccines prevent severe disease," she says.

Worse-case scenario

Another key question the current trials are too small to answer is whether a vaccine prevents people from catching and transmitting the virus. This might sound like a crucial feature of a vaccine but it isn't: a vaccine is designed to prevent people getting ill. It is, however, important because it is necessary (but not sufficient) to achieve herd immunity.

In fact, vaccines could, in theory, make matters worse. If they suppress disease but don't stop people from catching and shedding the virus, they effectively convert symptomatic cases into asymptomatic ones. That may lead to large numbers of infected people who aren't aware they have the virus going about their daily lives while releasing virus, rather than self-isolating. This "may paradoxically increase transmissions", the *Annals* paper says.

"A worst-case scenario is a vaccine that reduces disease while permitting viral shedding," wrote Marc Lipsitch at the Harvard T. H. Chan School of Public Health and Natalie Dean at the University of Florida in a recent perspective piece in *Science*. "This could fail to reduce transmission or conceivably even increase transmission if it suppressed symptoms."

REUTERS/LISI NIESNER

Yet another thing that the data so far cannot tell us for sure is whether the vaccines are completely safe. Pfizer, Moderna and the Gamaleya National Center all say they haven't seen any severe adverse reactions among participants, but are continuing to collect data to be sure that they won't occur.

Peter Marks, who directs the FDA's Center for Biologics Evaluation and Research, the body that evaluates applications for vaccine licences and emergency use authorisations (EUAs), has said that he needs to see safety data showing that no volunteer has had a severe adverse reaction within two months of receiving their second shot. The FDA can issue EUAs as a way to fast-track medical products in exceptional cases. Pfizer has said it will have collected this safety data in the coming week, at which point it will apply for one.

Nearly all adverse reactions ought to be picked up within six weeks of a second shot, says Offit, so side effects are probably less of a concern than efficacy, although rare side effects might take longer to spot (see "Phase IV trials", left).

There are a couple of other unknowns too. We don't know how people who have had the virus and recovered will respond to any of the vaccines. Pfizer has been vaccinating these so-called seropositive people but excluded their data from the latest analysis. We also don't know whether the vaccines will put pressure on the virus to mutate.

All in all, as Hodgson says, the seemingly simple question "does this covid-19 vaccine work?" is surprisingly hard to answer.

In the end, of course, this could all just be speculative bellyaching, and none of these potential problems will actually materialise. Thus far, we have seen interim results from three of the 12 vaccine candidates that have reached phase III trials. More will undoubtedly follow.

Jeremy Farrar, director of the Wellcome Trust, says we should think of vaccine development as the creation of a portfolio rather than the search for a single magic bullet. Weaknesses in one, such as not working well in older people, may be covered by strengths in others.

Despite her words of caution, Hodgson is optimistic about the future too. "There are more than 200 vaccines in development, which is a phenomenal number, and using a variety of vaccine technologies," she says. "It's nearly impossible to predict exactly when, but I think the likelihood is we will have a number of candidates that are efficacious."

So not quite yes, yes, yes! – at least not yet. But barring some disaster, we will eventually be able to have what the brave volunteers in the trials are having. ▮

The idea that a vaccine could return life to normal early next year is unlikely

200
or more coronavirus vaccines are in development

12
of these are in phase III trials

3
of which have published early results